Preoperative IMRT for soft-tissue sarcoma of the extremities and trunk

Studer, Gabriela ; Glanzmann, Christoph ; Maduz, Franziska ; Bode, Beata ; Fuchs, Bruno

Abstract: Background: The Canadian prospective randomized NCIC SR2 trial tested the sequence of radiation and surgery for extremity soft-tissue sarcoma. The trial was conducted in the era before intensity-modulated radiation therapy (IMRT) was clinically available. Similar disease control after preoperative and postoperative non-IMRT was found. However, the preoperative non-IMRT arm showed significantly less (persisting) late-term effects but increased (transient) wound complication rates compared to the postoperative non-IMRT arm (35% vs. 17%, P = 0.01). Consequently based on these results, preoperative radiation therapy was considered the preferred approach. Currently IMRT, with its option for highly conformal dose distribution that translates into better normal tissue sparing, is used as the general standard for sarcoma radiation therapy in most patients. Our hypothesis was that a lower wound complication rate after preoperative radiation therapy might be achievable in the IMRT era. Methods: We prospectively assessed our preoperative IMRT cohort (n=67 consecutive patients) treated between March 2008 and March 2016 with respect to wound complication rates. Results: Fourteen of 67 (21%) externally referred patients with recurrent (n=1) or incompletely resected disease (n=13), and 53 treatment-naive patients underwent planned preoperative radiation after core biopsy. After mean/-median 7.3/7 wk (3-12 wk), complete tumor resection was performed. Secondary revision was required in five of 67 (i.e., wound complication rate of 7%). Two local failures were observed so far. Conclusions: The presented results support our hypothesis that preoperative IMRT may lead to a reduced wound complication rate compared to that after postoperative and mainly preoperative non-IMRT techniques.

DOI: https://doi.org/10.1097/BCO.0000000000000665

Preoperative IMRT for soft-tissue sarcoma of the extremities and trunk: low rate of wound complications

Gabriela Studer, MD, HoD[ab], Christoph Glanzmann, MD[ab], Franziska Maduz, BScN[c], Beata Bode, MD[d] and Bruno Fuchs, MD[bc]

[a]Sarcoma Center, Department of Radiation Oncology, University Hospital Zurich, Switzerland
[b]Sarcoma Center, Surgical Department, Cantonal Hospital Lucerne, Switzerland
[c]Sarcoma Center, Department of Orthopaedics, Balgrist University Hospital, Zurich, Switzerland
[d]Sarcoma Center, Institute of Pathology and Molecular Pathology, University Hospital Zurich, Switzerland

ABSTRACT

Background:

The Canadian prospective randomized NCIC SR2 trial tested the sequence of radiation and surgery for extremity soft-tissue sarcoma. The trial was conducted in the era before intensity-modulated radiation therapy (IMRT) was clinically available. Similar disease control after preoperative and postoperative non-IMRT was found. However, the preoperative non-IMRT arm showed significantly less (persisting) late-term effects but increased (transient) wound complication rates compared to the postoperative non-IMRT arm (35% vs. 17%, $P = 0.01$). Consequently based on these results, preoperative radiation therapy was considered the preferred approach. Currently IMRT, with its option for highly conformal dose distribution that translates into better normal tissue sparing, is used as the general standard for sarcoma radiation therapy in most patients. Our hypothesis was that a lower wound complication rate after preoperative radiation therapy might be achievable in the IMRT era.

Methods:

We prospectively assessed our preoperative IMRT cohort (n = 67 consecutive patients) treated between March 2008 and March 2016 with respect to wound complication rates.

Results:

Fourteen of 67 (21%) externally referred patients with recurrent (n = 1) or incompletely resected disease (n = 13), and 53 treatment-naive patients underwent planned preoperative radiation after core biopsy. After mean/median 7.3/7 wk (3-12 wk), complete tumor resection was performed. Secondary revision was required in five of 67 (i.e., wound complication rate of 7%). Two local failures were observed so far.

Conclusions:

The presented results support our hypothesis that preoperative IMRT may lead to a reduced wound complication rate compared to that after postoperative and mainly preoperative non-IMRT techniques.

Key Words

IMRT, soft-tissue sarcoma, preoperative highly conformal radiation therapy, wound healing, postoperative complications

INTRODUCTION

The role of combined modality radiation therapy (RT) before or after surgery of large soft-tissue sarcoma (STS) is well established.[1–3] Based on the prospectively randomized Canadian NCIC SR2 trial,[4] disease control rates were similar after preoperative and postoperative RT, while the rate of wound complication was higher but mostly of no severe character in the preoperative RT arm (17 vs. 35%, [95% CI 5–30], $P = 0.01$). Based on the NCIC SR2 trial results, preoperative RT has been, in consequence, introduced as the standard procedure for STS at the own department. Smaller RT volumes and lower RT dose are characterizing the preoperative RT setting in STS (50 Gy in the preoperative versus 60-66 Gy in the postoperative setting). Postoperative RT volumes used to be larger than preoperative RT volumes, as surgically touched tissue, scars, and any drainage tunnels are considered to be included into the RT volume.

Radiobiologically, lower doses and smaller RT volumes each translate into fewer side effects. Postoperative RT includes, in consequence, two disadvantages from an RT perspective (higher dose, larger volume). Early RT side effects are characterized by their early and transient appearance, generally with complete healing after a few weeks. In contrast, late-term RT effects tend to rise months to years after RT completion and persist or even progress over years or decades. In consequence, late-term effects are of much more significance for patients than transient early side effects. With respect to late-term effects, the radiobiological inverse relationship between RT dose-volume and RT effects impacts mainly patients with large lesions.[5,6] Improved quality of life due to higher late-term tolerance after preoperative RT (i.e., less dose AND less RT volume!) with respect to skin alterations, tissue edema, fibrosis, bone fractures, and joint stiffness is reported.[4,7–9]

Financial Disclosure: The authors report no conflicts of interest.

Correspondence to Gabriela Studer, MD, HoD, Luzerner Kantonsspital, Spitalstrasse, Lucerne, Lucerne 6000, Switzerland
Tel: +41(0)412055800; fax: +41(0)412055804;
e-mails: gabriela.studer@luks.ch, gabriela.studer@usz.ch.

Wound complications represent early RT side effects. Wound complication rates were found to be higher in the lower extremity, especially in the thigh, as compared to the upper extremity.[9,10] These findings were from the historic era without IMRT techniques. Over the past approximately 15 yr, substantial advantages in RT dose distribution were achieved by the clinical implementation of IMRT techniques, translating into improved normal tissue sparing with comparable or better tumor dose coverage.

The surgical community has not yet widely adopted the practice of referring STS patients for preoperative RT because of the higher wound complication rates reported during the pre-IMRT era, and to a certain degree because of dissection on preirradiated tissue is often thought to be more challenging.

The aim of this analysis was to assess wound complication rates after preoperative IMRT. Our hypothesis was that reduced wound complication rates may be achievable by using IMRT as a preoperative RT technique.

MATERIALS AND METHODS

Informed consent was available for all patients. Ethical local committee approval was obtained for this analysis of our prospectively collected data set (which includes disease control parameters, treatment parameters, and treatment tolerance parameters).

Patients

A prospective cohort of 67 consecutive patients who were all operated and followed by the same surgeon (BF) received preoperative IMRT between March 2008 and March 2016 at the Department of Radiation Oncology, University Hospital Zurich. Exclusion criterion was previous RT at the same area. Authors GS and CG performed RT plan contouring and double-checking and were responsible for the dose distribution of the RT plans. All patients underwent highly conformal preoperative RT with 50 Gy in 25 fractions, followed by complete surgical resection. In one patient with planned R1 resection postoperative boost radiation therapy was performed (16 Gy in 8 fractions).

All included patients had confirmed histopathological diagnosis done by author BB before therapy (according to the WHO 7th Edition classification) either on reviewed samples of the external excisions or on regular core biopsies. Patient details are summarized in Table 1.

TABLE 1. Patient and disease characteristics

Parameters	n
Patients	67
Age, mean, median (range)	56, 58 (19-85) years
Gender (male : female)	38 : 27
Localization	
Upper leg	36
Lower leg	11
Axilla/shoulder/arm	9
Thoracal/abdominal trunk	10
Histopathological diagnosis	
Lipomatous tumors, N = 34 (51%)	
Atypical lipomatous tumor	9
Liposarcoma, dedifferentiated	2
Liposarcoma, myxoid	21
Liposarcoma, pleomorphic	2
Unclassified sarcomas, N = 19 (28%)	
Pleomorphic	17
Spindle cell	2
Myxofibrosarcoma	6
Leiomyosarcoma	3
Synovial sarcoma	3
Others (1 DFSP, 1 SEF)	2
Referred with "whoops lesions"	14 (21%)
GTV (mean, median (range)	402/261 cc (range, 0-1654 cc)
PTV (mean, median (range)	1320/1100 cc (range, 18-3908 cc)
Bolus (mean, median (range)	129/102 cc (range, 15-600 cc)

DFSP, dermatofibrosarcoma protuberans; GTV, gross tumor volume; PTV, planning target volume; SEF, sclerosing epithelioid fibrosarcoma.

Pretreatment Procedures

After completion of primary tumor staging (CT of the lung in all, including the abdomen in selected patients, and recent MRI of the primary lesion in all treatment-naive patients, and in all patients after "whoops" surgery), decisions regarding the indication for combined modality treatment were made at the weekly multidisciplinary sarcoma board joined by surgeons, radiation oncologists, oncologists, diagnostic radiologists, and pathologists familiar with sarcomas.

Preoperative RT

RT techniques were chosen with respect to the tumor size, anatomic extension, and tumor location (organs at risk) to reach optimal planning target volume (PTV) coverage while best sparing surrounding tissues. All plans were based on three-dimensional CT-calculations, using volumetric modulated arc therapy or IMRT techniques whenever superior to conformal three-dimensional RT techniques. This was assessed by comparative planning. In some patients, comparative planning was performed to identify the technique offering the individually best dose distribution. This so-called "plan comparison" resulted in conformal three-dimensional RT techniques as superior/equal approach in 19 patients with superficially located lesions ("IMRT-equivalent" dose distributions). Preoperative standard total dose of 50 Gy delivered in 25 fractions (5 fractions per week) with the 95% isodose encompassing the PTV, was delivered. The clinical target volume (CTV) was defined as follows: gross tumor volume (GTV) with a margin of 3 cm in the longitudinal and 1.5-2 cm (–3 cm if occult disease towards a compartment border is suspected) in the lateral direction. Peritumoral edema was included in all directions by the CTV but not in the GTV. Pretreatment MRI (image fusion whenever possible) was always used for GTV/CTV definition purposes. The PTV was defined as CTV plus 0-1 cm (depending on the RT [set up error/patient positioning and of the surrounding anatomical structures/natural borders like bone/fascia]).

Automatic calculation of the assessed GTV, PTV, and skin areas covered by bolus materials was provided by the Varian Treatment Planning System (TPS Eclipse™, Version 7.3.10, Varian Medical Systems, Palo Alto, CA) volume algorithm. Placement of large bolus material (1-cm thickness) to the skin in patients with tumor expansion close to or into the skin was applied in 62 of 67 patients (92%;

Table 1). The use of bolus materials aims to intentionally increase the dose to the covered skin towards full prescription dose instead of the lower entry dose achieved without bolus; this translates clinically into expectedly increased early skin reaction. The biopsy canal was covered with a small bolus to sufficiently treat potential microscopic spread due to previous biopsy.

Surgical Treatment

Surgery was performed 6 to 8 wk after completion of RT in 65 patients. Treatment delay occurred in two patients because of unrelated medical problems: one patient experienced a myocardial infarction after he received 40 Gy in 2.0 Gy/fraction and required a percutaneous coronary intervention with a stent implantation. He recovered well and was operated at 10 wk after the completion of the RT without any symptoms but with continuous aspirin medication; another patient's surgery was delayed due to the patient's preference. Preoperatively, all patients received at least three doses of cefuroxime intravenously. The surgical technique included resection of all macroscopic tumor in an en bloc fashion, including previous biopsy scars and drain sites, if present. The aim was to spare neurovascular structures with the principles established by the Toronto group, taking advantage of the biological barriers to accept close margins.[11] The sciatic nerve was preserved by entering the perineurium of the sciatic nerve proximally and distally of the tumor such that the perineurium was left with the tumor. Accordingly, the adventitia as well as the periosteum, if necessary, were dissected from the vascular structures and bone, respectively, and left with the tumor. In case of no biological barrier, we chose a 1- to 2-cm radial margin and longitudinally 4 to 5 cm. Special care was taken to achieve meticulous hemostasis during the entire surgery. Drains were routinely used and removed depending on fluid production usually between 24-48 hr after surgery. In patients who were referred to our institution after prior incomplete tumor excision, careful re-excision of the surgical bed and scar was performed. Wound complications were defined according to the Canadian Trial as requiring secondary operations or invasive procedures for wound care, use of vacuum-assisted closure, prolonged dressing changes, or infection within 120 days of surgery.[4]

The follow-up of all patients was regularly performed by author BF (surgeon) initially according to the healing process and the extent of surgery and after some weeks every 3 mo during the first 2 yr after treatment, then twice a year. All surviving patients are still in regular follow-up.

Statistics

Survival curves were performed using Kaplan Meier calculations [StatView® (Version 4.5; SAS Institute, Cary, NC, USA)].

RESULTS

Wound Complication Rate

At the time of surgery at a mean/median time of 7.3/7 wk after RT, none or mild residual early dermatitis was seen in all patients (grade 0-2 skin reaction according to CTCA Ev3).

Sixty-two of 67 (93%) patients experienced uneventful primary wound closure. Secondary revision was required in five of 67 patients (wound complication rate 7%). In three of these five affected patients, the tumor was located in the adductor muscle compartment. In the remaining two patients with initially uneventful healing, secondary wound breakdown without an apparent reason required revision.

Regarding the skin exposed to tumor dose in the five patients with wound complications, the skin area covered by bolus material was mean/median 207/182 cc, range 81 cc to 400 cc (higher values than the patients without wound complications with mean/median 138/119 cc, range 16 to 600; no statistics: unbalanced sample size). Also the GTV was mean/median larger in the affected five patients compared to unaffected individuals (510/402 cc, range 32 to 1380 cc vs. 396 to 294 cc, range 0 to 1654 cc).

Preoperative radiation allowed closer surgical margins to spare functionally important structures in the majority of patients according to the principles established by the Toronto group.[3,11–15] A safe biologic margin depends not only on the metric distance, but also on the biologic barrier. Close histopathologic metric margins were chosen depending on the type of biologic barrier and were as follows in this series: 0 to 1 mm in 40 of 58, 2 to 3 mm in 12 of 58, 5 to 35 mm in six of 58 patients with STC; 0-3 mm in nine of nine patients with atypical lipomatous tumor (ALT) (relation to mdm2 not necessary since included in the histopathologic definition of ALT), one patient had a planned positive margin resection.[11]

Disease Control

After a mean/median follow-up time of 37/33 mo (range 4-106), two local failures were observed, both in patients who presented with prior "whoops" lesions. Local control, distant metastasis-free survival, and overall survival rates for the 58 patients with malignant sarcoma (nine patients with atypical lipomatous histologies excluded) at 3 yr were 98%, 69% and 86%, respectively. Forty-five patients with high-grade sarcoma referred for primary treatment were all locally controlled (without any signs of local recurrence on MRI) when last seen. Nine of 67 patients diagnosed with ALT were interdisciplinarily decided to undergo combined modality treatment because of the large tumor size and/or close contact to the neurovascular bundle.

DISCUSSION

We found a wound complication rate of 7% in the presented cohort, and a local control rate of 100% in treatment-naive patients with preoperative IMRT for STS. The low wound complication rate found in our cohort was lower than the postoperative and mainly the preoperative non-IMRT arm of the Canadian prospective randomized NCIC SR2 trial (7% vs. 17% and 35%, respectively),[4] supporting our hypothesis.

In our department the publication of the NCIC SR2 trial results[4] led to an internal standard operation procedure change to preoperative RT. IMRT was used early after clinical implementation back in 2003. Our satisfactory interdisciplinarily achieved results motivated to the constitution of our sarcoma center and to the release of our national STS guidelines.[16]

Limitations of our analysis include the relatively small sample size and with respect to the disease control a still short follow-up time. Nevertheless, our results point towards a lower wound complication rate in a well-defined, single-center group of patients who were all homogeneously treated according to the same protocol by the same physicians.

In our patients with wound complications, a larger skin area with tumor dose was found as compared to the patients without wound complications. Baldini *et al*.[17] found tumor size and (often positively related) proximity to the skin to be significant predictors for major wound complications in univariate analyses. There are several other reports on wound complications after non-IMRT series. Tseng *et al*.[10] reported a wound complication rate of 36% for the lower extremity in a collective of 49 patients. These authors found no difference in terms of wound complication rates whether the primary surgeon or a reconstructive surgeon performed the wound closure. Cannon *et al*.[18] reported a wound complication rate of 34% for resection after preoperative RT of the lower extremity, applying the same definitions for wound complications as O'Sullivan *et al*.[4] after preoperative RT and tumor resection of the lower limb.

Preoperative (IMRT or non-IMRT) radiation therapy is favored by others because it uses less irradiation volume und dose, with potentially fewer long-term side effects for the patients. Virkus *et al*.[2] reported a wound complication rate of 26% after preoperative (conventional three-dimensional, i.e. non-IMRT) RT and surgical resection in the lower extremity. The authors considered wound complications as moderate when wounds required an operative irrigation and debridement with reclosure or wounds that had not closed after 3 months of local treatment, major when multiple operative interventions were necessary, and amputation as a third class of wound complications. Cheng *et al*.[19] compared preoperative with postoperative non-IMRT radiation and reported a wound complication rate of 31% in the preoperative compared to 8% in the postoperative subgroup (wound complication defined as any wound problem that required a secondary operation for treatment, resulted in a delay in RT of at least 1 mo, or a wound that did not heal and persisted for at least 6 mo). They did not report separate results for tumors of the upper and lower extremities. Mack *et al*.[20] assessed 75 patients also from the pre-IMRT era who received a shorter-course preoperative RT (30 Gy in fractions of 3.0 Gy per day in 10 days) combined with neoadjuvant chemotherapy and reported a wound complication rate of 16%. They considered a wound complication as major when a patient needed a reoperation and as minor when a patient developed a seroma, infection, or minor wound breakdown that could be treated by local wound care, antibiotics, or drainage. No separate report on complication rates for the upper extremity was given; however, the collective consisted of 73% of patients with tumors of the lower extremity. Overall, the wound complications in these series of preoperative RT ranged between 16% and 36%. Our result of 7% of wound complications compares favorably but is still lower than any reported. The type of RT used may be one explanation for the relatively high complication rate in these older series, and IMRT may improve it. Alektiar *et al*.[21] presented preliminary results on preoperative or postoperative IMRT of upper and lower extremity STS in 31 patients and found infectious and noninfectious wound complication rates of 13% and 10%, respectively. A recent phase-2 study performed by the Canadian trialists on wound complication rates of lower extremity STS showed no significant difference in wound complication rates after preoperative IMRT compared with non-IMRT in the NCIC trial (30.5 vs. 43%, $P = 0.6$).[22] Therefore, the authors speculated that IMRT alone may not represent the main factor influencing wound complications. Wang *et al*.[23] reported the results of the TROG-0630 Trial (extremity STS treated with image-guided RT to a reduced target volume, with preoperative IMRT in 75% of 79 eligible patients). Thirty-six percent (26/71 patients assessed for wound complications) experienced at least one wound complication (secondary operative debridement [25.5%], prolonged dressing changes [24%], readmission for wound care [21%]).[23]

Other reasons also may negatively affect wound complications. The interval to perform surgery after the last radiation treatment may be important. Whereas the group from Toronto found a trend towards a higher rate of wound complications in patients who had surgery after 6 wk (28% prior vs. 34% after; $P < 0.08$), this was not found in our results, with a mean interval of 7.3 wk and a wound complication rate of 7%; however, our small sample size and wound complication rates prevent forming reliable information on this topic.[3] Tumor localization may also be a predictor of wound breakdown,[24] with tumors in the adductor compartment of the thigh specifically being associated with wound break down. This also was confirmed by our series, with the tumor in four of five patients with wound complications being localized in the thigh.

The international community may define parameters such as size, volume, response to RT, etc. such that large patient numbers from different centers become comparable and small differences can be identified. One aspect to be kept in mind in preoperative sarcoma RT is certainly the often seen tumor volume change under RT,[25] requiring adaptive planning in certain patients (performed in two of 67 of our patients). It has been shown that the outcome of patients with STS indeed does differ even among international high-volume centers.[26,27]

In conclusion the presented results support our hypothesis that preoperative IMRT may lead to a reduction of wound complication rates compared to that after postoperative and mainly preoperative non-IMRT techniques.

REFERENCES

1. Rosenberg SA, Tepper J, Glatstein E, *et al*. The treatment of soft-tissue sarcomas of the extremities: prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. *Ann Surg*. 1982; 196:305–315.
2. Virkus WW, Mollabashy A, Reith JD, *et al*. Preoperative radiotherapy in the treatment of soft tissue sarcomas. *Clin Orthop Relat Res*. 2002; 397:177–189.
3. Biau DJ, Ferguson PC, Chung P, *et al*. Local recurrence of localized soft tissue sarcoma: a new look at old predictors. *Cancer*. 2012; 118:5867–5877.

4. O'Sullivan B, Davis AM, Turcotte R, *et al*. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. *Lancet*. 2002; 359:2235–2241.
5. Davis AM, O'Sullivan B, Turcotte R, *et al*. Trial NCICCTGR. Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. *Radiother Oncol*. 2005; 75:48–53.
6. Stewart AJ, Lee YK, Saran FH. Comparison of conventional radiotherapy and intensity-modulated radiotherapy for postoperative radiotherapy for primary extremity soft tissue sarcoma. *Radiother Oncol*. 2009; 93:125–130.
7. Zagars GK, Ballo MT, Pisters PW, *et al*. Preoperative vs. postoperative radiation therapy for soft tissue sarcoma: a retrospective comparative evaluation of disease outcome. *Int J Radiat Oncol Biol Phys*. 2003; 56:482–488.
8. Yang JC, Chang AE, Baker AR, *et al*. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. *J Clin Oncol*. 1998; 16:197–203.
9. Davis AM, O'Sullivan B, Bell RS, *et al*. Function and health status outcomes in a randomized trial comparing preoperative and postoperative radiotherapy in extremity soft tissue sarcoma. *J Clin Oncol*. 2002; 20:4472–4477.
10. Tseng JF, Ballo MT, Langstein HN, *et al*. The effect of preoperative radiotherapy and reconstructive surgery on wound complications after resection of extremity soft-tissue sarcomas. *Ann Surg Oncol*. 2006; 13:1209–1215.
11. O'Donnell PW, Griffin AM, Eward WC, *et al*. The effect of the setting of a positive surgical margin in soft tissue sarcoma. *Cancer*. 2014; 120:2866–2875.
12. Biau DJ, Weiss KR, Bhumbra RS, *et al*. Monitoring the adequacy of surgical margins after resection of bone and soft-tissue sarcoma. *Ann Surg Oncol*. 2013; 20:1858–1864.
13. Haas RL, Delaney TF, O'Sullivan B, *et al*. Radiotherapy for management of extremity soft tissue sarcomas: why, when, and where? *Int J Radiat Oncol Biol Phys*. 2012; 84:572–580.
14. O'Sullivan B, Griffin AM, Dickie CI, *et al*. Phase 2 study of preoperative image-guided intensity-modulated radiation therapy to reduce wound and combined modality morbidities in lower extremity soft tissue sarcoma. *Cancer*. 2013; 119:1878–1884.
15. Alektiar KM, Hong L, Brennan MF, *et al*. Intensity modulated radiation therapy for primary soft tissue sarcoma of the extremity: preliminary results. *Int J Radiat Oncol Biol Phys*. 2007; 68:458–464.
16. Brodmann S, Studer G, Zimmermann F, *et al*. Radiotherapie von Weichteilsarkomen der Extremitäten bei Erwachsenen. Behandlungsrichtlinien der Schweizer Gesellschaft für Radio-Onkologie (SRO). *Swiss Medical Forum*. 2015; 15:430–433.
17. Baldini EH, Lapidus MR, Wang Q, *et al*. Predictors for major wound complications following preoperative radiotherapy and surgery for soft-tissue sarcoma of the extremities and trunk: importance of tumor proximity to skin surface. *Ann Surg Oncol*. 2013; 20:1494–1499.
18. Cannon CP, Ballo MT, Zagars GK, *et al*. Complications of combined modality treatment of primary lower extremity soft-tissue sarcomas. *Cancer*. 2006; 107:2455–2461.
19. Cheng EY, Dusenbery KE, Winters MR, *et al*. Soft tissue sarcomas: preoperative versus postoperative radiotherapy. *J Surg Oncol*. 1996; 61:90–99.
20. Mack LA, Crowe PJ, Yang JL, *et al*. Preoperative chemoradiotherapy (modified Eilber protocol) provides maximum local control and minimal morbidity in patients with soft tissue sarcoma. *Ann Surg Oncol*. 2005; 12:646–653.
21. Alektiar KM, Brennan MF, Healey JH, *et al*. Impact of intensity-modulated radiation therapy on local control in primary soft-tissue sarcoma of the extremity. *J Clin Oncol*. 2008; 26:3440–3444.
22. Griffin AM, Dickie CI, Catton CN, *et al*. The influence of time interval between preoperative radiation and surgical resection on the development of wound healing complications in extremity soft tissue sarcoma. *Ann Surg Oncol*. 2015; 9:2824–2830.
23. Wang D, Zhang Q, Eisenberg BL, *et al*. Significant reduction of late toxicities in patients with extremity sarcoma treated with image-guided radiation therapy to a reduced target volume: results of Radiation Therapy Oncology Group RTOG-0630 Trial. *J Clin Oncol*. 2015; 33:2231–2238.
24. Moore J, Isler M, Barry J, *et al*. Major wound complication risk factors following soft tissue sarcoma resection. *Eur J Surg Oncol*. 2014; 40:1671–1676.
25. Dickie C, Parent A, Griffin AM, *et al*. The value of adaptive preoperative radiotherapy in management of soft tissue sarcoma. *Radiother Oncol*. 2017; 122:458–463.
26. Sanniec KJ, Swanson S, Casey WJ III, *et al*. Predictive factors of wound complications after sarcoma resection requiring plastic surgeon involvement. *Ann Plast Surg*. 2013; 71:283–285.
27. Pradhan A, Cheung YC, Grimer RJ, *et al*. Does the method of treatment affect the outcome in soft-tissue sarcomas of the adductor compartment? *J Bone Joint Surg Br*. 2006; 88:1480–1486.